American Association for Cancer Research

FINDING CURES TOGETHER℠

CICR May 2019 Newsletter

From the Editors

With:

Zhao-Kui Wan, PhD

Founder & CEO
Lynk Pharmaceuticals
Pudong, Shanghai
China

Iain DG Watson, PhD
Senior Research Scientist, Drug Discovery
Ontario Institute for Cancer Research
Toronto, Ontario
Canada

AACR Annual Meeting 2019 Webcasts Available

It was great to see so many chemistry-related researchers and those from other fields of cancer research recently at the AACR Annual Meeting 2019 in Atlanta, Georgia! View webcasts from this major event. We look forward to seeing many of you at next year's Annual Meeting in San Diego, California, April 24-29, 2020.

Each quarter, the editorial board selects an area to highlight from the broad range of topics that fall under the umbrella of chemistry in cancer research. Our topic this quarter is *antibody-drug conjugates*. CICR editorial board members Iain Watson and Zhao-Kui Wan have taken the lead in assembling an overview of the topic.

Antibody-drug conjugates (ADCs)

Antibody–drug conjugates (ADCs) aim to deliver potent therapeutic agents to desired tumor sites, while sparing healthy tissues from deleterious side effects. They are targeted biopharmaceuticals that combine the potent cytotoxic effects of a cancer drug with the selective targeting abilities of monoclonal antibodies. Often described as 'magic bullets', they have seen rapid recent progress as a new therapeutic class, with four recently approved agents and a large number of additional agents in clinical development.

ADCs consist of three components; an antibody that serves as the targeting and delivery system, a payload drug that kills the cancer cell, and a chemical linker through which the payload is attached to the antibody. Technological advancements may occur within each component and at each attachment point between the components.

The highly selective monoclonal antibody component (mAb) serves as the targeting agent, typically recognizing a highly and selectively expressed tumor-associated antigen that has little or no expression on normal healthy cells. This first component is responsible for the wide therapeutic window of ADCs, as the cytotoxic abilities of the payload drug are only unmasked upon recognition and internalization of the ADC by the target cancer cell.

The linker is the second key element of an ADC, attaching the payload to the targeting antibody. These biodegradable connectors may be non-cleavable or cleavable; in the latter, a particular bond (e.g. hydrazone, disulfide, peptide) is engineered to release the active drug under certain chemical or enzymatic conditions. Cleavable linkers may exert a subsequent bystander killing effect if the drug is then released from the targeted cell. In contrast, non-cleavable linkers result in active charged drug-linker agents that result from cellular degradation of the antibody, which are less likely to release from the targeted cell.

The final component is the drug payload, the choice of which represents a critical design element for any ADC. Thus far, cytotoxic payloads have dominated the field, with mechanisms of action such as tubulin binding (auristatines, maytansines), DNA double strand breakers (calicheamicin), DNA minor groove binders (pyrrolobenzodiazepines), TOPO1 inhibitors (camptothecin), and DNA alkylators (indolinobenzodiazepines, duocarmycins) all being studied clinically.

Mylotarg was the first ADC to be approved by the FDA. It received approval in 2000 for use in patients over the age of 60 with relapsed CD33-positive AML, under an accelerated process. However, due to safety concerns, Pfizer withdrew Mylotarg from the market at the request of the FDA. More recently, Pfizer reapplied for approval on the basis of further clinical trial results and analysis; approval was again granted in 2017. To date, there are four clinically approved ADCs: Mylotarg (gemtuzumab ozogamicin, Wyeth/Pfizer), Adcetris (brentuximab vedotin, Seattle Genetics/Millennium), Kadcyla (trastuzumab emtansine, Genentech/Roche), and Besponsa (inotuzumab ozogamicin, Wyeth/Pfizer), but there are many more in clinical development. As ADCs are a relatively new drug class, research in this area is still growing and expanding.

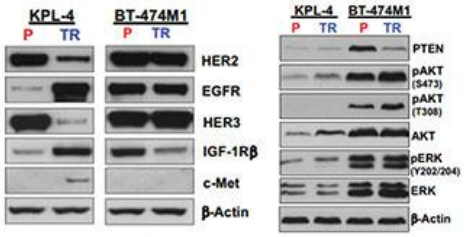
The interest of the oncology scientific community in ADCs can be seen by their increasing appearance at the Annual Meetings of the AACR. ADCs are also emblematic of the increasingly diverse role of the chemist in drug discovery. The challenges inherent in drug-conjugate development provide new opportunities for the

chemist working in cancer research. The elevating role of this area can be seen in the recent *From Chemistry to the Clinic* Session, which focused on *Advances in Antibody Drug Conjugates*, at the 2017 AACR Annual Meeting. Indeed, there are increasing numbers of ADC presentations at Annual Meetings, ranging from presentation of clinical data to new molecule disclosures. In this issue, we highlight some of these presentations, including the disclosure of the structure of the novel drug-conjugate BT1718 by Bicycle Therapeutics at the *New Drugs on the Horizon* session of the 2018 AACR Annual Meeting in Chicago, as well as the disclosure of the a BCL-X_L ADC ABBV-155 at a similar session in this year's meeting in Atlanta. These packed sessions are yearly highlights of the CICR section of the AACR Annual Meetings, with multiple newly disclosed agents disclosed every year.

In this issue of the Newsletter, we have presented recent examples of some of the many areas in which chemical research is impacting the discovery and development of ADCs. Articles describing the application of new payloads are described, including the selection of both cytotoxic and targeted antineoplastic agents. Natural products are undoubtedly linked to ADC research and we present recent research describing their importance and chemical manipulations allowing them to be successfully paired to their respective antibodies. Relative to simple and low molecular weight small molecule drugs, the synthetic challenges are greatly increased when working with large ADCs of increased molecular complexity. Development and manufacturing challenges are highlighted in a series of articles that describe the discovery, development and manufacturing of a clinical ADC. We are also pleased to highlight the work of Dr. Kyoji Tsuchikama, an Assistant Professor at the University of Texas Health Science Center at Houston. Dr. Tsuchikama's group is heavily involved in the development of novel linker technologies for ADCs and his work is highlighted in this issue's Profile of an Early-Career Researcher.

Molecular Cancer Therapeutics

This recent article from *Molecular Cancer Therapeutics (MCT)* related to this issue's theme may also be of interest:



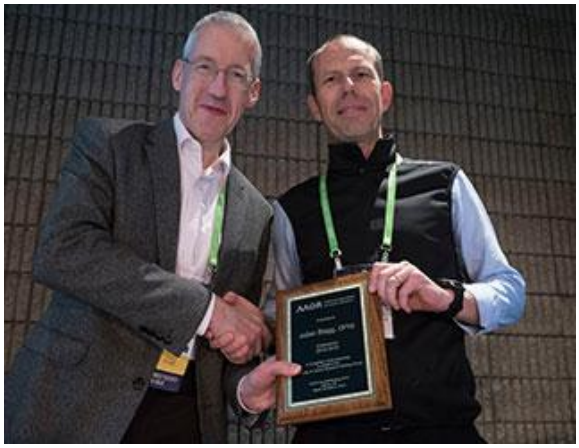
Mechanisms of Acquired Resistance to Trastuzumab Emtansine in Breast Cancer Cells
Guangmin Li, et al.
DOI: 10.1158/1535-7163.MCT-17-0296
Published July 2018

Resistance to Trastuzumab Emtansine (T-DM1) poses a challenge in therapy for HER2-positive breast cancer. A better understanding of the molecular mechanisms of primary and acquired resistance to T-DM1 is particularly important for developing new therapeutic strategies. In this study, the authors established T-DM1 resistant cells and identified different features contributing to the resistance of these cells. Their findings show the complexities of T-DM1 resistance in that the two models they studied showed little overlap in identified resistance mechanisms; KPL-4-derived resistance was mostly due to drug efflux and decreased HER2, while BT-474-derived resistance was due to loss of PTEN expression. In the latter example, combining T-DM1 with the PI3K inhibitor GDC-0941 synergistically killed BT-474-derived T-DM1-resistant cells. Taken together, the study identifies avenues of T-DM1 resistance and outlines potential strategies for overcoming this resistance in the clinic.

News from the CICR Steering Committee

Contributed by CICR Chair, Andrew J. Phillips, PhD
President and Chief Executive Officer
C4 Therapeutics
Watertown, Massachusetts

CICR Events at the AACR Annual Meeting 2019



It was a very successful Annual Meeting for chemistry-related programming. Overflow audiences were garnered for the "Chemistry to the Clinic" three-part session March 30 and the "New Drugs on the Horizon" two-part session March 31. Additionally, a very well-attended CICR Town Hall Meeting and Reception provided for great networking and interaction following the "New Drugs on the Horizon, Pt. 2" session. At left, I, on behalf of the CICR Working Group, congratulated CICR Past Chair, Prof. Julian Blagg, on a productive tenure as head of the working group for 2018-2019, and wished him the best in future endeavors. See the photos of the CICR Town Hall.

CICR Town Hall at the "New Horizons in Cancer Research" Conference in Shenzhen, China

Former CICR Steering Committee Member and present CICR Editorial Board Member, Dr. Zhao-Kui (ZK) Wan of Lynk Pharmaceuticals, hosted a successful and informative event and luncheon, Sunday, May 5, 2019, at the "New Horizons in Cancer Research Conference" in Shenzhen, China. Great interaction among the attendees took place during a luncheon after a brief presentation on the CICR Working Group. Hopefully, more collaboration with our Chinese colleagues on CICR events will result

after this stimulating conference program. This Town Hall was also featured in a recent article in the AACR blog, *Cancer Research Catalyst*.

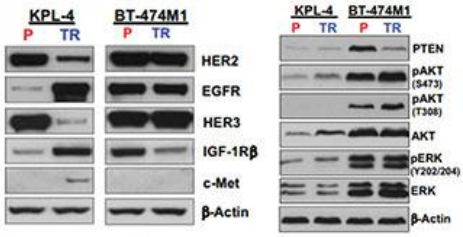
Plan to Attend the CICR Town Hall Meeting and Reception at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics Oct. 26-30, 2019 in Boston, Massachusetts

I look forward to seeing all CICR members at this exciting conference and to welcoming you to the CICR Town Hall on Sunday, Oct. 27, 2:30-3:30 p.m., for an update on CICR initiatives. Come and enjoy some cordial networking with colleagues known and yet-to-be-known at the reception after a brief program. Refreshments will be served. For more details and to register for this exciting conference, see here. Abstract submission deadline: Monday, July 22.

AACR Awards 2020 Nominations Now Being Accepted

All CICR members are encouraged to submit nominations for the 2020 AACR Awards, to include the AACR Award for Outstanding Achievement in Chemistry in Cancer Research and an **inaugural** award for 2020, the AACR Award for Outstanding Achievement in Basic Cancer Research that is intended for an early-career investigator. The deadline for nominations is **Aug. 1, 2019**. The deadline for nominations for the AACR June L. Biedler Prize for Cancer Journalism will remain sometime in November 2019. Details on this award's nomination process will be posted shortly.

Selected Research and Review Highlights



Mechanisms of Acquired Resistance to Trastuzumab Emtansine in Breast Cancer Cells
Guangmin Li, et al.
DOI: 10.1158/1535-7163.MCT-17-0296
Published July 2018

Resistance to Trastuzumab Emtansine (T-DM1) poses a challenge in therapy for HER2-positive breast cancer. A better understanding of the molecular mechanisms of primary and acquired resistance to T-DM1 is particularly important for developing new therapeutic strategies. In this study, the authors established T-DM1 resistant cells and identified different features contributing to the resistance of these cells. Their findings show the complexities of T-DM1 resistance in that the two models they studied showed little overlap in identified resistance mechanisms; KPL-4-derived resistance was mostly due to drug efflux and decreased HER2, while BT-474-derived resistance was due to loss of PTEN expression. In the latter example, combining T-DM1 with the PI3K inhibitor GDC-0941 synergistically killed BT-474-derived T-DM1-resistant cells. Taken together, the study identifies avenues of T-DM1 resistance and outlines potential strategies for overcoming this resistance in the clinic.

Improved therapeutic window in BRCA-mutant tumors with an ADC
Zhong A et al, Mol Canc Ther 2019; 18:89-99.
http://mct.aacrjournals.org/content/18/1/89.long
In order to combat the persistent issue of a low therapeutic index resulting from the commonplace use of highly cytotoxic compounds as ADC payloads, a research team from MedImmune and Astrazeneca have further explored the use of pyrrolobenzodiazepine dimers (PBD) as alternative warheads. PDBs are known to form minor groove DNA cross-links, which are repaired by gene products such as BRCA1 and 2. Based on a hypothesis that PBD-based ADCs will be more effective in cells that have defective repair processes, the team evaluated the efficacy of ADCs that use an anti-5T4 antibody conjugated with a PDB dimer in a variety of mouse models. They observed improvements in sensitivity when BRCA 1 and 2 were knocked out, and this translated into PDX models made from patient samples with BRCA mutations. Further, they found that the combination of a PARP inhibitor with a lower dose of the ADC produced tumor regressions and was well tolerated. This work points to a clinical application in which patients with BRCA mutations may achieve a response with a wider therapeutic window.

Bcl-XL ADC enters the clinic
Phillips A C, From *New Drugs on the Horizon 2*, AACR Annual Meeting 2019, April 1, 2019

Numerous Antibody-Drug Conjugates were presented at the Annual AACR meeting in Atlanta, showcasing advancements in the application of the technology to an ever-expanding array of targets. One of the ADC highlights of the meeting was certainly the first-time disclosure of ABBV-155, a first-in-class conjugate based on a BCL-X_L inhibitor. With the company's BCL-X_L programs halted due to clinical and preclinical toxicological findings – in particular, preclinical cardiotoxicity – AbbVie turned to the use of an ADC to limit systemic exposure of the inhibitor. The antibody choice was driven by the observation that B7H3 and BCL-X_L are often both expressed in settings expected to demonstrate cancer dependence on BCL-X_L. The discovery and optimization strategy thus focused on attaching an exquisitely potent BCL-X_L inhibitor to a B7H3 antibody; the linker between the two was optimized to balance solubility, permeability, efficacy, and safety. ABBV-155 showed some efficacy as a monotherapy in certain lung cancer cell lines, and was shown to be very effective *in vivo* in combination with taxanes, generating durable xenograft regressions and on-target disruption of the BCL-X_L::BIM complex. Importantly, the ADC is well tolerated in preclinical models, with only limited cardiotoxicity relative to the BCL-X_L inhibitor. ABBV-155 is now in clinical development.

KSP inhibitor conjugates with a legumain-mediated cleavage
Lerchen H-G, et al Chem: Eur J 2019; 25:1-7.
https://onlinelibrary.wiley.com/doi/abs/10.1002/chem.201900441

One of the primary challenges with the ADC concept is controlling "leaky" toxicity; that is, residual effects from the cytotoxic payload, especially if cleaved in appropriately. To combat this, Bayer have explored novel payloads based on Kinesin Spindle Protein (KSP) inhibitors. The choice of the cytotoxic agent for antibody-drug conjugates (ADC) has thus far been primarily high molecular weight cytotoxic natural products. As reported last year (https://doi.org/10.1002/anie.201807619), a team from Bayer AG describe the use of kinesin spindle protein inhibitors (KSPi) as a novel antibody drug conjugate (ADC) payload. The KSPi molecules described are a new pyrrole subclass that act on KSP, an ATP-dependent motor protein involved in the separation of centrosomes in the G2/M phase of the cell cycle. The KSPi-ADCs were shown to be potent and selective in vitro and demonstrated in vivo efficacy in a panel of tumor models. Another advancement was recently published and presented at this year's Annual Meeting in Atlanta. In this new work, the researchers achieve further control of the safety profile by engineering the conjugate with a cleavage site specifically mediated by the lysosomal endopeptidase legumain, which is often associated with tumors. With this additional measure, the novel kinesin payload was reduced in normal tissue, while still achieving efficacy in tumors.

Nicotinamide phosphoribosyltransferase inhibitor as a novel payload for antibody–drug conjugates
Karpov AS et al, *ACS Med Chem Lett* 2018;9(8):838–842.
https://pubs.acs.org/doi/10.1021/acsmedchemlett.8b00254

Nicotinamide phosphoribosyltransferase (NAMPT) inhibitors target the conversion of nicotinamide to nicotinamide mononucleotide, the rate-limiting step that controls intracellular NAD^+ concentration. Several NAMPT inhibitors advanced into the clinic, but their utility was limited by their on-target toxicities. With this point in mind, the authors applied NAMPT inhibitors as a novel non-antimitotic payload for antibody-drug conjugates (ADCs). The NAMPT inhibitors were linked at the solvent-exposed end via cleavable and non-cleavable linkers to c-Kit monoclonal antibodies. The resulting anti-c-Kit ADCs demonstrated *in vivo* efficacy in the c-Kit positive gastrointestinal stromal

tumor GIST-T1 xenograft model in a target-dependent manner. This study shows the potential for the application of ADC payloads with novel modes of action which may increase therapeutic options for this drug modality.

Design and synthesis of Tesirine, a clinical antibody-drug conjugate pyrrolobenzodiazepine dimer payload
Tiberghien A et al, *ACS Med Chem Lett* 2016;7(11):983-987.
https://pubs.acs.org/doi/10.1021/acsmedchemlett.6b00062

Scale-up synthesis of Tesirine
Tiberghien A et al, *Org Proc Res Dev* 2018;22(9):1241-1256.
https://pubs.acs.org/doi/10.1021/acs.oprd.8b00205

An alternative focus for route design for the synthesis of antibody-drug conjugate payloads
Tiberghien A et al, *J Org Chem* 2019;ASAP.
https://pubs.acs.org/doi/10.1021/acs.joc.8b02876

This trio of papers highlights the synthetic approaches used in the discovery and development of a clinical antibody-drug conjugate (ADC). In the first, the authors describe the design and synthesis of rovalpituzumab tesirine (Rova-T, Abbvie/Stemcentryx) a DLL-targeting antibody conjugated to tesirine, a pyrrolobenzodiazepine dimer that exhibits cytotoxic behavior as a result of binding to the DNA minor groove. The approach to drug conjugation is described, involving the capping of one of the reactive imines with a cathepsin B-cleavable valine-alanine linker. In the second paper, the authors describe the development of the synthetic route into a manufacturing process to enable the production of large amounts of Tesirine, the payload for Rova-T. Finally, the authors describe the special challenges associated with ADC manufacture. In particular, the analysis focuses on the high cost of containment facilities required when manipulating highly cytotoxic advanced ADC intermediates. These containment processes can involve controlled air handling, such as airlocks or gloveboxes for handling materials as well as time-consuming cleaning and decontamination procedures. The paper describes how a route design that focuses on the minimization of these steps may result in a significant reduction in the cost of goods. The synthesis and manufacturing of ADCs clearly leads to different challenges then conventional small-molecule therapeutics. As more ACDs are progressed into the clinic, confronting these issues will facilitate the development ADCs broadly as a therapeutic class.

Total synthesis in search of potent antibody-drug conjugate payloads. From the fundamentals to the translational
Nicolaou KC, Rigol S, *Acc Chem Rev* 2019;52:127-139.
https://pubs.acs.org/doi/10.1021/acs.accounts.8b00537

In clinical antibody drug conjugates (ADCs) such as Mylotarg, Adcetris, Kadcyla, and Besponsa, natural products have furnished the cytotoxic payloads. Recent research into ADCs has led to questions surrounding the choice of molecules for these payloads. The act of natural product total synthesis not only furnishes the ability to replicate rare naturally occurring compounds, but also offers a unique opportunity to design and synthesize analogues for evaluation as ADC payloads. The authors describe total synthesis endeavors that led to ADC analogues, such as molecules of the calicheamicin, uncialamycin, tubulysin, trioxacarcin, epothilone, shishijimicin, namenamicin, thailanstatin, and disorazole families of compounds. Synthetic changes can result in higher potency, or in less complexities in their use as payloads. The

review is an excellent highlight of the power of total synthesis and natural product research and their impact on modern medicine.

The discovery of BT1718: A novel bicyclic peptide drug conjugate drug conjugate for the treatment of solid tumors expressing MT1-MMP
Keen NJ, From *New Drugs on the Horizon 1*, AACR Annual Meeting 2018, April 15, 2018
https://webcast.aacr.org/p/2018annual/8729

Bicycle Therapeutics disclosed the structure of their clinical drug conjugate BT1718, at last year's heavily attended *New Drugs on the Horizon* session at the AACR Annual Meeting in Chicago. Termed bicycle toxin conjugates (BTCs) or peptide drug conjugates, this class of drugs resemble ADCs, but use bicycle peptides as the targeting agent instead of antibodies. Bicycles are bicyclic peptide drugs (1.5-2 kDa) that are structurally constrained by a small molecule scaffold that is irreversibly reacted at three points with the amino acid side chains of the molecule, folding and constraining the rotational ability of the peptide into a 3D-structure. The result of this conformational restriction is a peptide that has small molecule-like pharmacokinetic properties. Using phage display and directed evolution, bicycles can be developed into extremely potent and selective targeting molecules. BT1718 is a BTC targeting MT1-MMP, a surface metalloproteinase highly expressed in solid tumors. The drug uses a non-cleavable linker to attach DM1, a thiol-containing maytansinoid – also the drug used in the clinically approved ADC Mylotarg. BT1718 has an improved ADME and PK profile versus approved ADCs, with a drastically lower half life and improved tumor localization. This compound was effective in regressing MT-MMP expressing patient derived lung adenocarcinoma models, and is currently in clinical trials. The presentation shows how durable and effective the drug conjugate concept is and how varying the targeting component can significantly change the overall properties of the therapeutic agent.

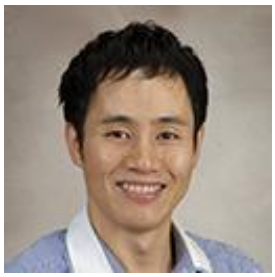
A non-PROTACs Brd4 degrader
Blake RA, From *Next Generation Small Molecules: From Hits to Leads to Candidates,* AACR Annual Meeting 2019, April 2, 2019

NOTE: Webcast is paid-access only and work is not published. For paid-only access, see the second presentation here.

With PROTACs technology rapidly proliferating through the cancer drug discovery community, scientists are learning to also be on the lookout for additional, and perhaps unanticipated, means of inducing protein degradation. At the 2019 AACR Annual Meeting in Atlanta, Genentech describe GNE-0011, a propargyl amine-based JQ1 derivative. This compound was shown not only to bind to Brd4 and inhibit Myc expression, but it, surprisingly, also potently reduces Brd4 protein levels. Interestingly, despite the lack of an E3-ligase-recruiting moiety, the degradation of the protein was shown to be dependent on ubiquitination and proteasomal function. The exact mechanism of this induction is currently unknown.

Profile of an Early-Career Researcher

Kyoji Tsuchikama, PhD



Kyoji Tsuchikama, PhD
Associate Member/Assistant Professor
The University of Texas Health Science Center at Houston
McGovern Medical School, Institute of Molecular Medicine
Houston, Texas

Antibody-drug conjugates (ADCs) are an emerging class of chemotherapeutic agents for cancer therapy. Promising clinical outcomes, with 4 FDA-approved ADCs and more than 70 ADCs in clinical trials, have attracted a great deal of attention from many researchers and clinicians. Dr. Kyoji Tsuchikama is a principal investigator leading a medicinal chemistry lab at the University of Texas Health Sciences Center at Houston (UTHealth). One of his research interests is directed towards establishing novel chemical platforms for effective targeted therapeutics, including ADCs. The engine of his laboratory, driving their effort in complex ADC research, is the diverse expertise and background of his lab members, which include organic chemistry, peptide chemistry, medicinal chemistry, chemical biology, pharmacology, radiochemistry, and skills for performing animal studies.

Dr. Tsuchikama studied organic chemistry, with a focus on transition metal-catalyzed reactions, during his undergraduate and graduate work with Prof. Takanori Shibata at Waseda University in Japan. After earning a Ph.D. in organic chemistry in March 2010, he received fellowship support from the Japan Society for the Promotion of Science (JSPS) to begin postdoctoral work on bacterial quorum sensing, under supervision of Prof. Kim D. Janda at The Scripps Research Institute. With experience at the interface of chemistry and biology in hand, Dr. Tsuchikama started his independent career at UTHealth in July 2014. He has received support for his research programs from the UT System (Reagents' Health Research Scholars Award) and the Department of Defense (Breast Cancer Research Program Breakthrough Award).

His laboratory has been committed to developing novel linker technologies for constructing efficacious ADCs. One of their recent achievements is a method for enzymatic conjugation using branched linkers that can accommodate two payload units (*Organic & Biomolecular Chemistry* **2017**, 15, 5635-5642). Despite extensive efforts to advance ADC linker and conjugation chemistries, most of the commonly used ADC linkers possess linear structures and can accommodate only single payloads. The clinical potential of branched ADC linkers that can accommodate multiple payloads has not been fully explored. In particular, although apparently easy to achieve, it has been technically challenging to construct homogeneous ADCs using branched linkers, due largely to the lack of efficient conjugation methods.

Dr. Tsuchikama and his lab members have developed an efficient method for conjugating branched linkers using microbial transglutaminase (MTGase). MTGase-mediated linker conjugation has been previously used to attach simple linear linkers to the side chain of glutamine 295 within the antibody heavy chain. Tsuchikama and his lab have now optimized conjugation conditions and linker design to achieve quantitative installation of relatively bulky branched linkers containing two azide groups, using the same enzyme. Subsequent coupling of payload modules by click reactions provides homogeneous ADCs with higher drug-to-antibody ratios (DARs)

than conventional linear linkers, thus enhancing ADC cytotoxic potency with a minimal modification to the antibody structure. The lab is currently developing second-generation branched linkers that enable modular assembly of various homogeneous ADCs equipped with two different payloads.

Another notable achievement by his group is the discovery of a glutamic acid-valine-citrulline tripeptide linker (*Nature Communications* **2018**, 9:2512). A dipeptide comprised of valine-citrulline (VCit) is used as an enzymatically-cleavable linker in approximately 50% of ADCs that have been clinically approved or tested. This linker releases conjugated payloads in a traceless manner upon cathepsin-mediated cleavage in the target cancer cell. While stable in human plasma, VCit linkers are unstable in mouse plasma, due to susceptibility to the carboxylesterase Ces1c. Considering that most preclinical studies use mouse models, this instability creates an obstacle for the preclinical evaluation of the therapeutic potential and safety profiles of VCit-based ADCs. Dr. Tsuchikama and co-workers discovered that a glutamic acid-valine-citrulline (EVCit) linker can significantly improve ADC stability and efficacy in mouse models. A model anti-HER2 ADC constructed using this linker exhibited much greater *in vivo* stability than the corresponding VCit-based ADC, which rapidly lost payload molecules due to premature linker cleavage. Further, the EVCit ADC showed significantly improved therapeutic efficacy in xenograft mouse models of human breast cancer compared with the VCit variant. The use of the EVCit linker could serve as a simple, but powerful, solution to salvage many types of ADCs that were previously abandoned at the preclinical evaluation stage due to linker instability in mice. These findings also highlight the potential of this novel ADC linker to minimize failure rates in future preclinical studies.

In collaboration with many cancer biologists and immunologists, ongoing work in the Tsuchikama group is further refining these novel linker technologies to generate next-generation ADCs for difficult-to-treat cancers and other diseases.

Spotlight on World News

Please Note: Discussion of FDA approvals for this issue are limited to new chemical entities approved to treat cancer since the release of the previous CICR Newsletter (February 2019).

Clinical failure of antibody-drug conjugate Rova-T
There was a recent clinical failure with Rova-T, a rovalpituzumab tesirine antibody-drug conjugate (ADC) in small cell lung cancer trial (SCLC). Seen as one of the next generation of ADCs, the asset was the most advanced candidate acquired by AbbVie in their 6 billion dollar acquisition of Stemcentrx in 2016. The TAHOE study was assessing Rova-T (rovalpituzumab tesirine) as a second line therapy for patients with SCLC and the data monitoring committee recommended stopping enrollment after observing shorter overall survival in the Rova-T arm. The design and development of this ADC is described in the research highlights section of this month's CICR Newsletter.
Sources: FierceBiotech, In The Pipeline

AstraZeneca invests in Daiichi antibody-drug conjugate
AstraZeneca is paying 1.35 billion to Daiichi Sankyo to jointly develop trastuzumab deruxtecan, an antibody-drug conjugate (ADC), with an additional 5.5 billion in potential sales and milestone payments. This ADC combines a topoisomerase I inhibitor with a HER2-targeting antibody. The drug is currently in studies to treat patients with breast and gastric cancers and the companies plan to file for approval later this year.
Sources: C&E News, Reuters

Bayer pumps up Cambridge
The Boston Globe reports that Bayer plans an expansion of its currently very small work force in Cambridge, Massachusetts. They are planning to conduct research in a new MIT-constructed building right off of Main Street, in the heart of Kendall Square. This news is especially welcome, as Bayer is otherwise in the middle of a massive global job contraction.
Source: Boston Globe

Triple threat for advanced pancreatic cancer
In results highlighted at the 2019 AACR Annual Meeting, clinicians from the Parker Institute at the University of Pennsylvania report that the combination of PD-1 checkpoint inhibition and CD40 immunotherapy along with chemotherapy produced tumor regressions in 20 of 24 patients tested in a recent trial. These remarkable results in a cancer type that has been historically ranked among the most difficult to treat represent a major advancement of the use of immunotherapy – as this method, too, has not typically seen success in pancreatic cancer. The work was based on preclinical

research carried out by Dr. Robert H. Vonderheide (U. Penn.), and occurred as part of a collaboration with Bristol-Meyers Squib and Apexigen, Inc.
Source: Parker Institute

Daiichi Sankyo and AstraZeneca strike deal on HER2 ADC
The Japanese pharma company Daiichi Sankyo and global giant Astrazeneca recently announced a development and commercialization deal centered on Daiichi Sankyo's anti-body drug conjugate based on the combination of [fam-] tratuzamab and deruxtecan. This ADC has been the flagship oncology asset for Daiichi Sankyo, and its development will now be accelerated by the agreement. Under the terms of the deal, achievement of all milestones will garner up to $5.5 billion in payments, in addition to the $1.35 billion upfront money paid to Daiichi Sankyo from AstraZeneca. While the companies will share the development burden globally, Daiichi Sankyo will retain exclusive rights to the compound in Japan.
Source: Cision

Mixed results for cancer research in proposed US 2020 budget
Under the terms of the 2020 budget proposal by United States President Donald Trump, the Food and Drug Administration (FDA) will receive a boost of $631 million compared with the 2019 US budget, which may help to accelerate the drug approval process. However, the National Institutes of Health (NIH) will see its third straight significant budget reduction (as much as $5 billion pulled from its coffers), with unfortunate effects on the National Cancer Institute (NCI). This organization is proposed to suffer a $900 million budget reduction, which represents an ~15% decrease from last year. As might be expected, several research-based organizations have leveled heavy criticism at this budget proposal.
Source: Fierce BioTech

Upcoming Conferences

See the AACR Meetings and Workshops Calendar for more conferences.

102nd Canadian Chemistry Conference and Exhibition
June 3-7, 2019, Quebec City, Canada

EFMC-ACSMEDI: Medicinal Chemistry Frontiers 2019
June 10-13, 2019, Krakow, Poland

2nd Anglo-Nordic Medicinal Chemistry Symposium
June 11-14, 2019, Hotel Comwell Borupgaard, Snekkersten, Denmark

Gordon Research Conference in Heterocyclic Compounds 2019
June 16-21, 2019. Newport, RI, USA

Gordon Research Conference in Cancer Nanotechnology: Bridging the Translational Gap in Cancer Nanotechnology
June 23-28, 2019, Mount Snow, West Dover, Vermont

55th International Conference on Medicinal Chemistry (RICT 2019)
July 3-5, 2019. Nantes, France

NCI Chemical Biology Consortium Symposium at Vanderbilt
July 10, 2019. Nashville, TN, USA

Gordon Research Conference in Computer-Aided Drug Design 2019
July 14-19, 2019, West Dover, Vermont

Gordon Research Conference in Organic Reactions & Processes 2019
July 21-26, 2019. Easton, MA, USA

Gordon Research Conference in Natural Products & Bioactive Compounds 2019
July 28 – August 2, 2019. Andover, NH, USA

Gordon Research Conference in Medicinal Chemistry 2019
August 4-9, 2019. New London, NH, USA

258th ACS National Meeting & Exposition
August 25-29, 2019. San Diego, CA, USA

BrazMedChem2019
September 1-4, Pirenopolis – Goias, Brazil

EFMC-ASMC '19: EFMC International Symposium on Advances in Synthetic and Medicinal Chemistry
September 1-5, 2019, Athens, Greece

20th SCI/RSC Medicinal Chemistry Symposium
September 8-11, 2019, Churchill College, Cambridge, UK

Fifth CRI-CIMT-EATI-AACR International Cancer Immunotherapy Conference: Translating Science into Survival
September 25 - 28, 2019, Paris, France

Cancer Research UK-AACR Joint Conference: Engineering and Physical Sciences in Oncology
October 15 - 17, 2019, London, England

AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutic
October 26-30, 2019, Boston, MA, USA

Canadian Cancer Research Conference
November 3-5, 2019. Ottawa, ON Canada.

Third FBDD Down Under
November 12-15, Mellbourne, Australia

AACR Annual Meeting 2020
April 24-29, 2019. San Diego, CA.

Funding Opportunities

2019 CSCO Young Investigator Travel Awards

The AACR in partnership with the Chinese Society for Clinical Oncology (CSCO) is awarding travel awards to the CSCO Annual Meeting in Xiamen, China in September 2019. Please click on the above title for further details. This Award includes:
Complimentary registration to the CSCO Annual Meeting
Accommodations for up to four nights
$1,000 USD for travel expenses
Application Deadline: 7/19/2019

AACR-Cancer Research UK Transatlantic Fellowships

Grant Amount: $400,000 USD Letter of Intent Deadline: 7/25/2019 Application Deadline: 10/9/2019 Decision Date: 1/2020
Start of Grant Term: 2/1/2020
Grant Duration: 4 years

AACR-Johnson & Johnson Lung Cancer Innovation Science Grants

Grant Amount: $1,000,000 USD Application Deadline: 7/19/2019 Decision Date: 11/2019
Start of Grant Term: 12/1/2019
Grant Duration: 3 years